Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Hacein-Bey-Abina S, Hauer J, Lim A, et al. Efficacy of gene therapy for X-linked severe combined immunodeficiency. N Engl J Med 2010;363:355-64.

Supplementary material

Supplementary Patients and Methods

Patients

Patient 3, who presented with persistent splenomegaly caused by a disseminated Bacillus Calmette-Guerin infection, failed to reconstitute his T-cell compartment due to the progenitor cells' trapping in the spleen. After splenectomy, he successfully received a MUD (matched unrelated donor) HSCT 8 months after gene therapy, according to the protocol.

Patient 9, who was treated in Australia, received $1x10^6$ cells/kg and had insufficient T cell reconstitution (460 CD3+ per mm3 at 5 months). He developed neurologic deterioration, gastrointestinal dysfunction and infections which were typical of a poorly reconstituted patient with SCID. He showed thereafter a progressive decline in immune function as well as a progressive reduction in total lymphocyte counts. He was engrafted with a 9/10 antigen matched unrelated donor 26 months after gene therapy and showed a low T-cell reconstitution i.e 400 CD3+ per mm3 9 months after transplantation. His clinical course was complicated by chronic GvHD, colitis, persisting neurological dysfunction and recurrent infections. He died from fungal pneumonia 18 months after the allograft [1].

Study design

S.Hacein-Bey-Abina, A. Fischer and M.Cavazzana-Calvo designed the study. A. Lim, C. Picard, G.P.Wang, C.Martinache, F. Rieux-Laucat, S.Latour, B.H.Belohradsky, L.Leiva, R. Sorensen, M.Debré, J.L.Casanova and S.Blanche gathered the data. S.Hacein-Bey-Abina, A. Lim, C. Picard, G.P.Wang, F. Rieux-Laucat, S.Latour, L.Leiva, A.Durandy, F.D.Bushman, and J.Hauer analysed the data. S.Hacein-Bey-Abina, C. Picard, J.Hauer, F Rieux-Laucat, S.Latour, A.Durandy, F.D.Bushman and M.Cavazzana-Calvo vouch for the completeness of the data and analyses. S.Hacein-Bey-Abina, A. Fischer and M.Cavazzana-Calvo wrote the manuscript. S.Hacein-Bey-Abina, A. Fischer and M.Cavazzana-Calvo decided to publish the paper.

Methods

Lymphocyte phenotypes and functions and TCR beta, alpha, gamma and delta chain repertoires were analyzed as described elsewhere[2-5]. Patients' B cells were analyzed for affinity maturation and cytokine + CD40L-induced class switch recombination [6]. Signal joint T-cell receptor excision circles (TREC) (sjTRECs; δRec-ψjα) were determined using a real-time quantitative polymerase chain reaction (Q-PCR)[7]. The TREC content was expressed in copies per $1x10_5$ peripheral blood mononuclear cells (PBMCs).

The control value (established in 20 healthy individuals) was between 150 and 2500 copies/10_5 PBMCs.

Naive and memory T-cell subpopulations were sorted by flow cytometry using fluorescence-labeled monoclonal antibodies against CD45RA+ CD4+ and CD45RO+CD4+, respectively. Ligation-mediated PCR was used to sequence vector integration sites in these selected populations [8]. Provirus integration over time was analyzed in a Taqman Q-PCR assay (Applera France) [3].

Supplementary Results

Clinical outcome

Lung infections cleared within the first 60 days after therapy and did not recur in Patients 1, 2, 7, 8 and 10. Protracted diarrhea resolved in Patients 1, 2 and 10, enabling parenteral nutrition to be discontinued within 3 to 4 months after therapy. Patient 7's pre-existing B-lymphoproliferative disease resolved 3 months after gene therapy. Patient 6's disseminated VZV infection was controlled as soon as the genetically modified T cells appeared in the peripheral circulation.

T cell characteristics

Long-term immune function

In order to determine whether distinct T-cell effectors were present in the patients' blood, available samples were screened against surrogate markers for Th1 (IFNγ), Th2 (IL-4) [9-11]. Patients 1 and 8 (tested at 117 and 85 months after therapy, respectively) showed similar proportions of IFNγ and IL-4 secreting CD4+ T cells (after activation by phorbol myristate acetate and ionomycin) as control cells (data not shown).

B cells and antibody responses

Two years after gene correction, somatic hypermutation frequencies in the IgM V region genes (VH3-23) of CD27+ B cells were found to be slightly below normal in 3 patients (Patients 1, 2, and 4) since 1.4, 1.3 and 1.9% of the nucleotides were mutated in the analyzed clones, respectively (control range: 2.3 to 6.5%). CD27+ B cells from Patient 2 were analyzed again 10 years after gene therapy and yielded a frequency of 2.6%. We also analyzed class switch recombination in treated patients to establish the respective role of γc-dependant and γc-independent cytokines in immunoglobulin production. Patient 2' B cells showed some proliferation in vitro in response to IL-4 plus CD40 ligand (CD40L), but a strong proliferation to IL-13 plus CD40L (6000 cpm versus 45000 cpm, respectively). In vitro IgE production in response to these 2 cytokines also showed a discrepancy with a lower level (but still considered normal) obtained after IL-4 stimulation than after IL-13 stimulation with respectively: 9676 pg/ml versus 25180 pg/ml. Patient 1's B cells, like those of Patient 2, showed a mild proliferative capacity (8000 cpm) but an absence of IgE secretion in response to IL-4 plus CD40L stimulation, but showed a normal response to IL-13. Patient 5's B cells showed no IgE secretion in response to IL-4 while a strong response to IL-13 was observed ie, 1357 pg/ml versus 50480 pg/ml respectively**.**

Supplementary Discussion

Comparison of the long term immune function among groups of immunodeficient patients treated by gene therapy on the one hand and HSCT on the other, is difficult given the small number of patients treated with gene therapy. In HSCT, early CD4+ T-cell counts and naive T-cell counts are predictive of late immune T-cell reconstitution [12]. It was low in only 1out of 8 patients in our series versus 31.6% in cases treated with HSCT reported by Neven et al. In our series, patient 6 fulfills this prediction since CD4+T-cell counts were initially low; this patient also received the lowest number of transduced cells. Patient 6 also has defective long term thymic output as assessed by low total CD4+, low CD31+/CD45RA+/CD4+ and low TRECs. Eight years after treatment, no clinical impact is evident.

Strikingly, another patient (P1) showed a decline in long term thymic output contrasting with high early T- cell parameters. A hypothesis currently being investigated is the possible partially transdominant negative effect of the endogenous mutated γc chain expressed by patient 1. Persistence of mutated γc chain might alter the physiological γc chain function in homeostatic conditions.

In addition to points discussed in the main text, the persistence of TREC+ naive T cells despite the disappearance of transduced functional stem cells in patients' bone marrows is reminiscent of the setting in some SCID-X1 patients who undergo HSCT without myeloablation. No donor B cells and myeloid cells can be detected in many of these individuals, whereas donor naive T cells are present [12-15]. Overall, our data are compatible with the hypothesis that thymus niches can be occupied by gene-transduced progenitors with self-renewal capacity [16].

In the long term, γc(+) B cells were no longer detected. Accordingly, most antibody responses to recall antigens were no longer detectable. Nevertheless, isohemagglutinins (IgM isotype) and responses to *Streptococcus pneumoniae* were at least partially preserved. Memory B cells were detected at a low frequency including switched memory B cells and above normal IgG and IgA levels were detected in 5 out of 8 patients.

Overall this residual B cell function was sufficient to avoid recurrent mucosal infections and made immunoglobulin replacement unnecessary in 5 patients. Patients' B cells were also able to undergo somatic hypermutations (SHM) which take place in the germinal centers (GCs) of lymphoid organs and which are driven by T cell signals. Intimate interaction between B cells and follicular T helper cells (TFH) is required for SHM to occur but γc-dependent cytokines are dispensable at this step. IL-21 is a key factor for the survival of memory B cells generated in GCs, and for the maintenance of the quality of the antibody response. The IL-21/γc axis defects are likely responsible for the fact that persistence of normal levels of memory B cells as well as sustained production of antibodies to vaccine antigens are both compromised by the absence of genetically-modified B cells [17-22].

These data are similar to those observed in SCID-X1 patients who underwent HSCT without myeloablation and indicate that despite an absence of IL21-mediated B cell activation / maintenance, [21, 22], γc-independent pathways are preserved, sustaining some B cell response, notably perhaps T-independent antibody responses and extrafollicular B cell activation [21]. In conclusion, these finding indicate that full humoral responses with normal levels of long term memory B cells and stable production of high affinity Ag-specific Abs can only be achieved by stable bone marrow engraftment of genetically modified stem cells, a state that would seem to require myeloablative conditioning regimen, as in the setting of allogeneic HSCT.

Supplementary References

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Suppl. Table. 1: Characteristics of leukemia in 4 patients

	Age at therapy (months)	T-ALL (months)	Follow-up (months)	CD34+γc+ cells infused ($x10^6$/kg)	Time of first CR (weeks)	Clinical status	Chemotherapy regimen	Leukemia phenotype	Insertion sites	Chromosomal Abnormalities	Notch Mutation (aa residue)	CDKN2A/P16 /ARF Deletion
P4	1	30	60	18	-	Died	DCLSG	Mature T-cell	LMO2	t(6,13)	-	+
P5	3	34	112	20	2	A.W., CR	CCSGT	Late cortical T-cell	LMO2	SIL-TAL, trisomy10	1593F/S	-
P7	11	68	105	4.3	3	A.W., CR	FRALLE 2000BT	Late cortical T-cell	CCND2	0	-	+
P10	8	33	88	11.3	1	A.W., CR	I-BFM-SG	Late cortical T-cell	LMO2, BMI-1	0	1707A/P	-

A.W: Alive and Well. **CR** : Complete remission. **B-LPD**: B-lymphoproliferative disease
DCLSG: Deutch Childhood Leukemia Study Group; **CCSGT**: Children's Cancer study Group T-ALL protocol ; **FRALLE 2000 BT**: French Acute Lymphoblastic Leukaemia (FRALLE2000BT) protocol; **I-BFM-SG**: International –BFM-Study-Group
Search for mutation or rearrangement for BCR/ABL, NUP214/AB , Hox11/ TLX1, HOX11L2/TLX3 and CALM-AF10 was negative in all 4 cases.
LMO2: LIM domain only 2 gene on chromosome 11, CCND2: cyclin D2 gene, BMI-1: gene in the polycomb group.

Suppl. Table. 2: B cells characteristics and antibodies responses

	controls	P1		P2		P5		P6***		P7***		P8		P10***	
		<3y	Last FU	<3y	Last FU	<3 y	Last FU	<3y	Last FU	<3y	Last FU	<3y	Last FU	<3 y	Last FU
Diphtheriae toxoid*	**>0.1 IU/ml**	+	-	+	-	-	-	ND	ND	ND	ND	+	-	ND	ND
Tetanus toxoid*	**>0.1 IU/ml**	+	-	+	-	-	-	+	ND	-	ND	+	-	+	ND
Polio viruses*	**>4 IU/ml**	+	-	+	-	-	-	+	ND	-	ND	+	-	+	ND
S. pneumoniae**	**>4 fold increase in titer**	ND	+	+	+	+	-	ND	ND	ND	ND	-	-	+	ND
Haemophilus ** influenzae (type b)	**>1µg/ml**	+	ND	+	+	+	-	ND	ND	ND	ND	-	-	ND	ND
Isohemagglutinins	**> 1:8**	1:64	1:16	1:32	1:64	1:4	ND	1:256	1:256	1:1	ND	1:4	-	1:4	ND
CD19+ γc+ cells (%)	**100**	0.9	<0.01	1.1	<0.01	2	<0.01	ND	<0.01	ND	<0.01	1	<0.01	1	ND
IL 21-dependent IgA response	**> 5000 ng/ml**	ND	-	ND	-	ND	-	ND	-	ND	-	ND	-	ND	ND
Memory B cells # (%CD27+CD19+)	**>10%**	3	2	9	30	7	3	5	9	4	ND	3	12	ND	8

*Antibodies against poliovirus antigens, tetanus toxoid and diphtheria toxoid, were first found at protective values as evaluated three months after the third immunization in all patients except patient 5. However in all of them, this initially protective response declined to negative values when tested 1 year after vaccination.

**All patients have been immunized with *Streptococcus pneumonia*e and *Haemophilus influenza*e one year after gene therapy. Antibodies are tested against a mix of 23 *Streptococcus pneumoniae* serotypes.

***Patients 6, 7 and 10 have not been evaluated for antibodies persistence given that IVIg has been restarted for them.

The values for CD27+/CD19+ memory B cells were determined at 2 years and at last follow-up.

Last FU: Last follow-up; y: years; ND: not done

Supplementary Figure Legends

Suppl. Figure 1: TCR Vβ repertoire analysis after gene therapy

The immunoscope profile's horizontal axis indicates the CDR3 length (in amino acids) and the vertical axis displays the arbitrary fluorescence intensity of the runoff products. The numbers on each profile correspond to the frequency of the corresponding family representation for TCR Vβ or Vα (IMGT nomenclature).

TCRVβ immunoscope profiles for 5 representative Vβ families in Patients 1 until 108 months, P2 until 121 months, P6 until 84 months, P8 until 93 months, **(A)** and Patients 5 until 112 months, P7 until 101 months, and P10 until 81 months, **(B)**. Each panel shows CDR3 length distribution profiles for Vβ2, Vβ7, Vβ11, Vβ20 and Vβ25 families at different time points (M = months post-gene therapy). P7 displayed at 101 months a similar CDR3 rearrangement in Vβ7 family than the one observed at the time of leukemia. This peak has therefore been analyzed and fortunately showed a different sequence than the pathological clone.

Suppl. Figure 2: TCR Vα repertoire analysis after gene therapy

Immunoscope profiles for CDR3 size for all the 33 TCR Vα gene families in healthy control, Patient 2 at 121 months and Patient 8 at 93 months post-therapy (A) Patient 5 at 112 months and Patient 7 at 101 months (B). All the CDR3 length distributions were Gaussian unless for P7 who still showed less diverse repertoire shortly after chemotherapy discontinuation.

Suppl. Figure 3:

Taqman quantification of the Vδ (upper panel) and Vγ (lower panel) families in T cells from a control subject (black) and from Patients 1 (yellow), P2 (orange), P5 (blue), P6 (pink), P7 (deep blue) P8 (green) and P10 (grey) in the most recent sample collected to date.

Suppl. Figure 4: T cell proliferative responses and NK cell subset

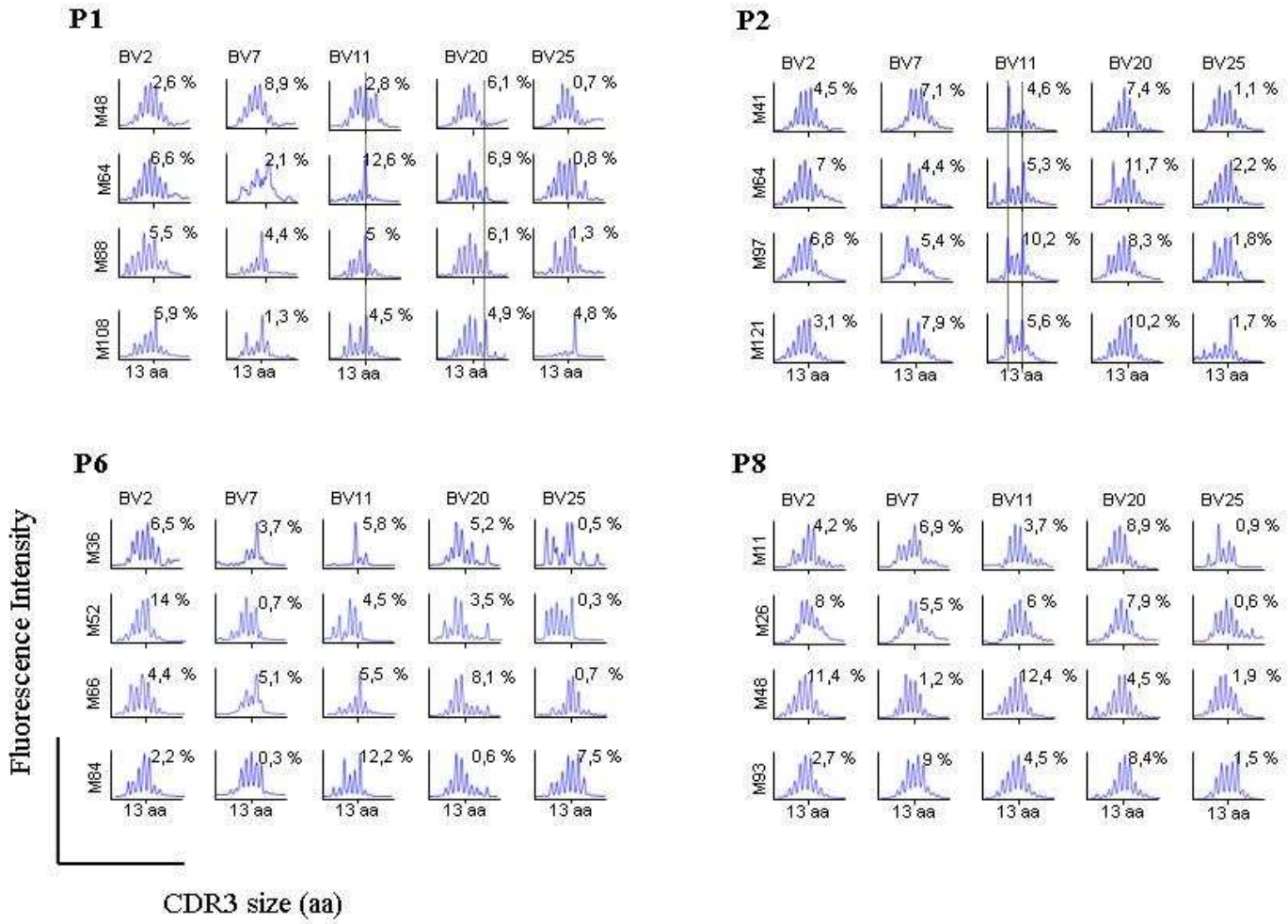
(A) Change over time in T cell proliferative responses in P1, P2, P6, P8 (left panel) and P7, P10 (right panel) following stimulation with phytohemagglutinin (PHA). Dashed line indicates normal values which represent the 5^{th} centile of values observed in normal controls.

(B) Change over time in absolute CD56+CD3- NK cell absolute counts (per cubic millimeter of whole blood and as measured by flow cytometry). Shaded area indicates reference values for age-matched controls.

Suppl. Figure 5: Retroviral integration sites analysis in memory and naive T cells from Patients 2 and 8.

Tests were carried out on samples taken 102 months (Patient 2) or 73 months (Patient 8) post-gene therapy. The bar graphs specify the integration sites by the nearest gene. The presence of an asterisk means that the integration site lies outside the indicated gene, whereas integration sites lacking an asterisk are within the indicated gene. Grey indicates all other low abundance sites. (A) Patient 2, naive T-cells (left) and memory T-cells (right). (B) Patient 8, naive T-cells (left) and memory T-cells (right).

Suppl.Fig.1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P1
BV2
BV7
BV11
BV20
BV25
M48
M64
M88
M108
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8,9 %
2,8 %
6,1 %
0,7 %
6,6 %
2,1 %
12,6 %
6,9 %
0,8 %
5,5 %
4,4 %
5 %
6,1 %
1,3 %
5,9 %
1,3 %
4,5 %
4,9 %
4,8 %
13 aa
P2
M41
M64
M97
M121
4,5 %
7,1 %
4,6 %
7,4 %
1,1 %
7 %
4,4 %
5,3 %
11,7 %
2,2 %
6,8 %
5,4 %
10,2 %
8,3 %
1,8%
3,1 %
7,9 %
5,6 %
10,2 %
1,7 %
P6
M36
M52
M66
M84
6,5 %
3,7 %
5,8 %
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0,5 %
14 %
0,7 %
4,5 %
3,5 %
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4,4 %
5,1 %
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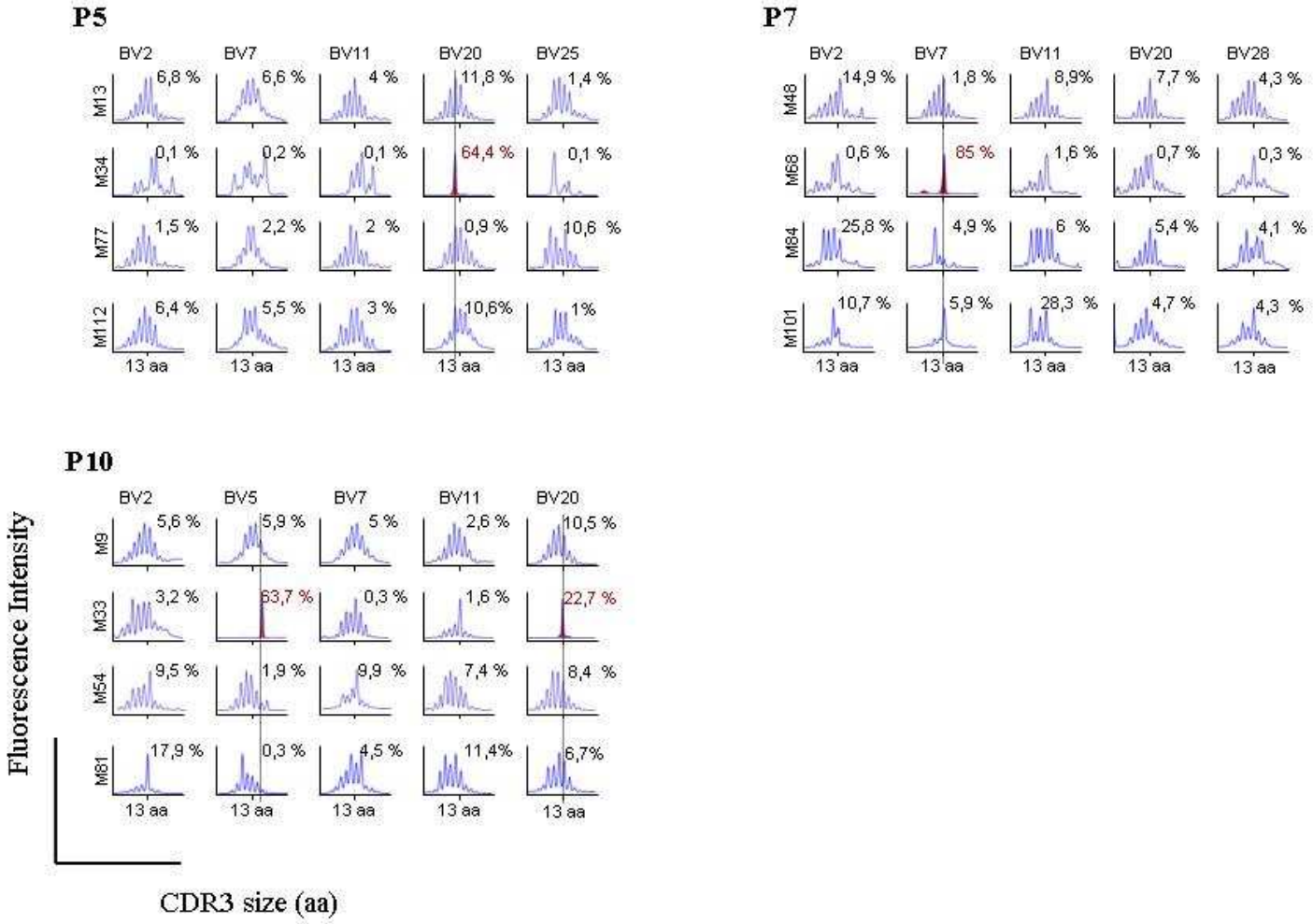
8,1 %
0,7 %
2,2 %
0,3 %
12,2 %
0,6 %
7,5 %
P8
M11
M26
M48
M93
4,2 %
6,9 %
3,7 %
8,9 %
0,9 %
8 %
5,5 %
6 %
7,9 %
0,6 %
11,4 %
1,2 %
12,4 %
4,5 %
1,9 %
2,7 %
9 %
4,5 %
8,4%
1,5 %
Fluorescence Intensity
CDR3 size (aa)

B


P5
BV2
BV7
BV11
BV20
BV25
M13
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6,6 %
4 %
11,8 %
1,4 %
M34
0,1 %
0,2 %
0,1 %
64,4 %
0,1 %
M77
1,5 %
2,2 %
2 %
0,9 %
10,6 %
M112
6,4 %
5,5 %
3 %
10,6%
1%
13 aa
P7
BV2
BV7
BV11
BV20
BV28
M48
14,9 %
1,8 %
8,9%
7,7 %
4,3 %
M68
0,6 %
85 %
1,6 %
0,7 %
0,3 %
M84
25,8 %
4,9 %
6 %
5,4 %
4,1 %
M101
10,7 %
5,9 %
28,3 %
4,7 %
4,3 %
13 aa
P10
BV2
BV5
BV7
BV11
BV20
M9
5,6 %
5,9 %
5 %
2,6 %
10,5 %
M33
3,2 %
63,7 %
0,3 %
1,6 %
22,7 %
M54
9,5 %
1,9 %
9,9 %
7,4 %
8,4 %
M81
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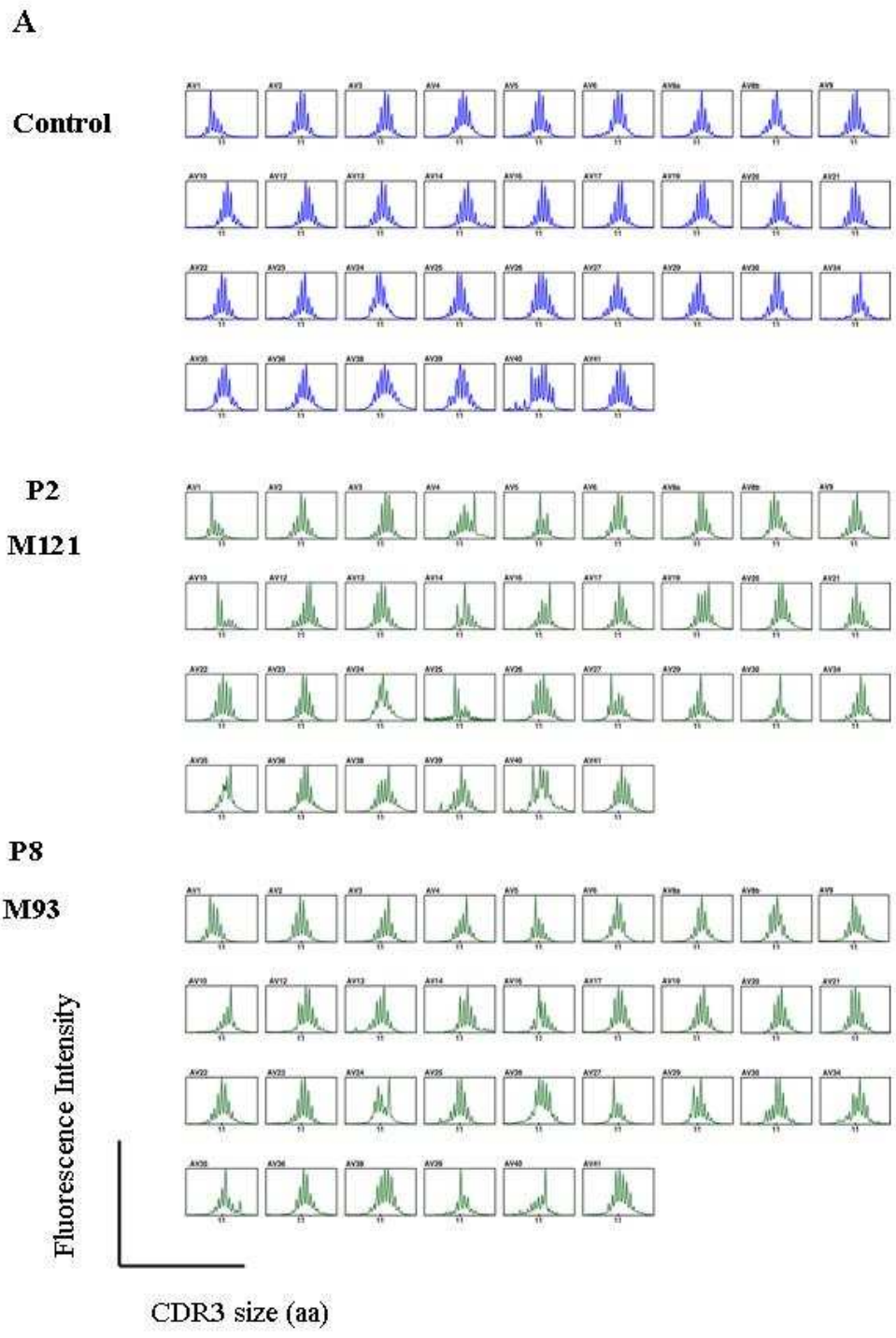
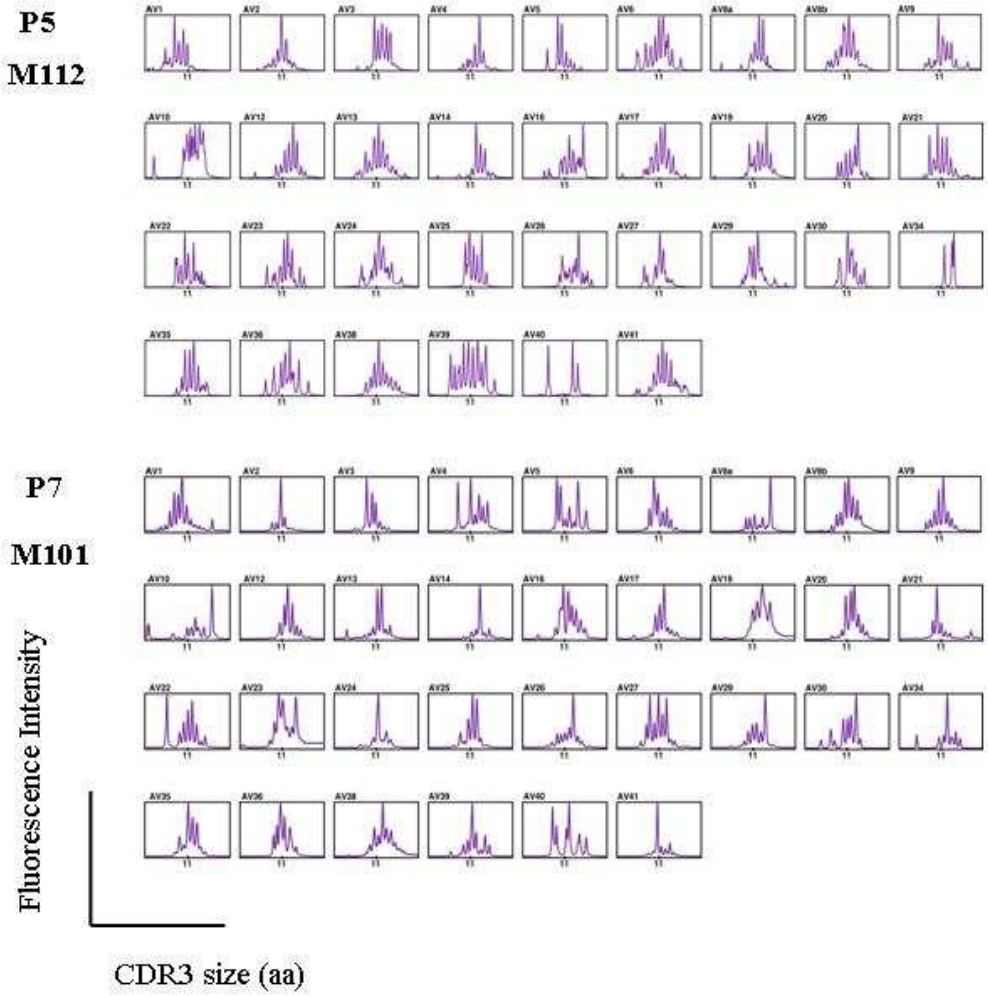
4,5 %
11,4%
6,7%
13 aa
Fluorescence Intensity
CDR3 size (aa)

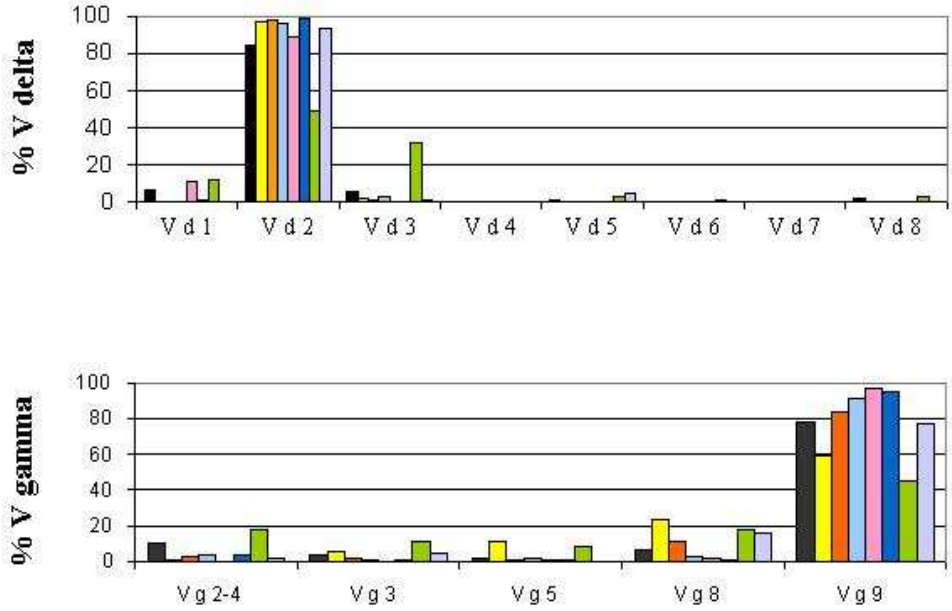
Suppl.Fig.2


A
Control
P2
M121
P8
M93
Fluorescence Intensity
CDR3 size (aa)

B



Suppl. Fig. 3


% V delta
100
80
60
40
20
0
Vd1
Vd2
Vd3
Vd4
Vd5
Vd6
Vd7
Vd8
% V gamma
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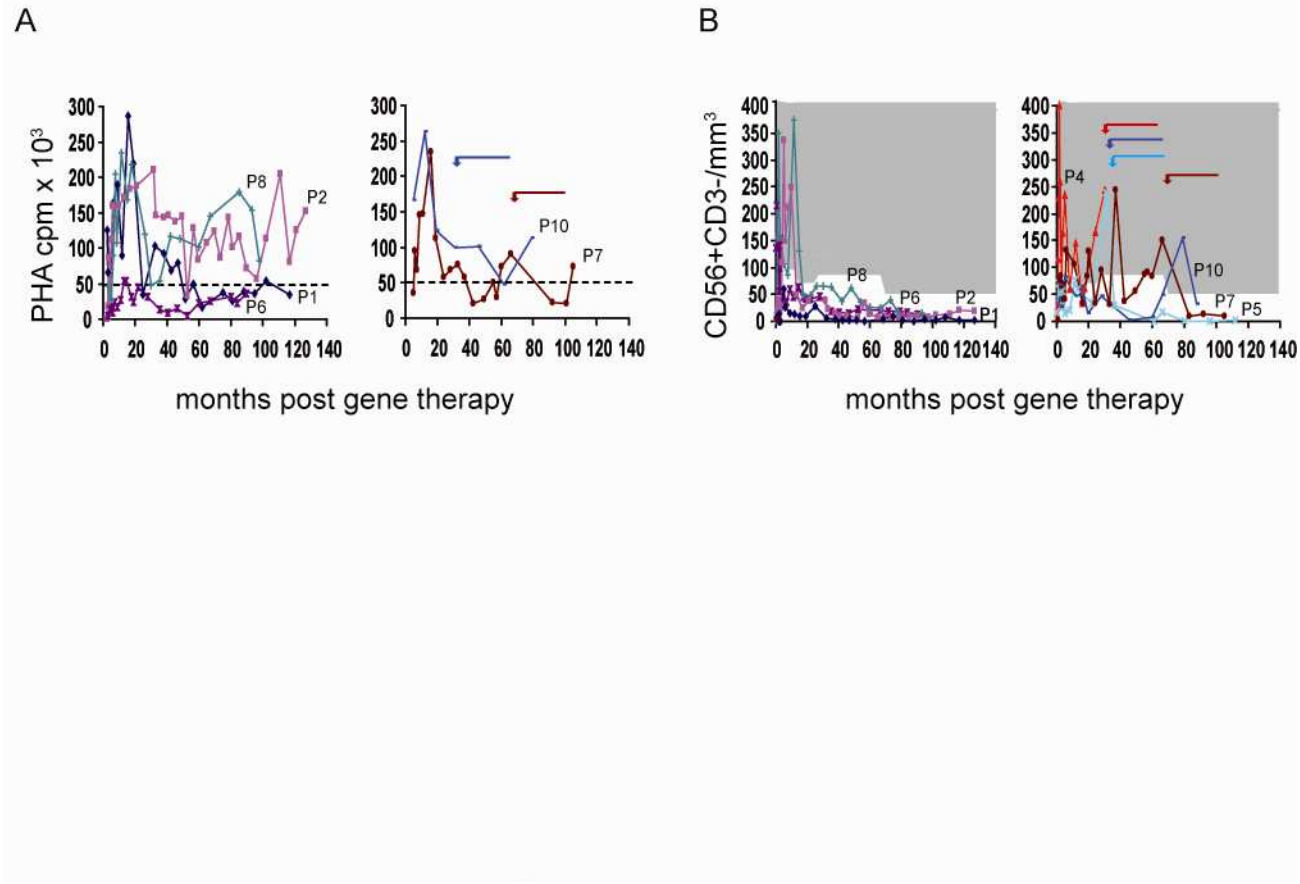
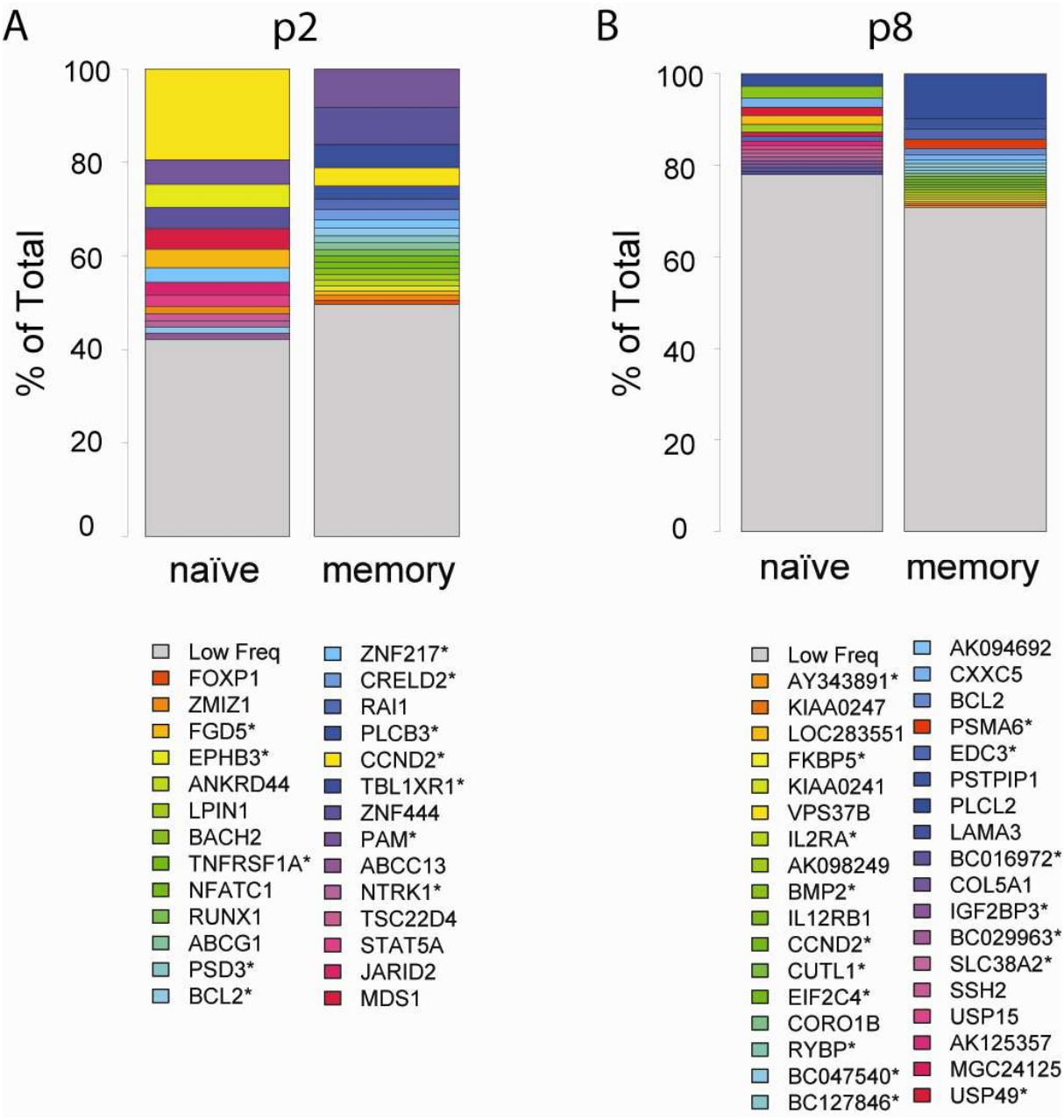
80
60
40
20
0
Vg2-4
Vg3
Vg5
Vg8
Vg9

Suppl. Fig.4


A
PHA cpm x 10³
P8
P2
P6
P1
P10
P7
months post gene therapy
B
CD56+CD3-/mm³
P8
P6
P2
P1
P4
P10
P7
P5
months post gene therapy

Suppl. Fig. 5


A
p2
100
80
60
40
20
0
% of Total
naïve
memory
Low Freq
FOXP1
ZMIZ1
FGD5*
EPHB3*
ANKRD44
LPIN1
BACH2
TNFRSF1A*
NFATC1
RUNX1
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PAM*
ABCC13
NTRK1*
TSC22D4
STAT5A
JARID2
MDS1
B
p8
100
80
60
40
20
0
% of Total
naïve
memory
Low Freq
AY343891*
KIAA0247
LOC283551
FKBP5*
KIAA0241
VPS37B
IL2RA*
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IL12RB1
CCND2*
CUTL1*
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CORO1B
RYBP*
BC047540*
BC127846*
AK094692
CXXC5
BCL2
PSMA6*
EDC3*
PSTPIP1
PLCL2
LAMA3
BC016972*
COL5A1
IGF2BP3*
BC029963*
SLC38A2*
SSH2
USP15
AK125357
MGC24125
USP49*